REMARKS

Response to the Office Action

In response to the Office Action dated June 11, 2010, Applicants respectfully submit the Remarks, and reconsideration is respectfully requested. Claims 15, 17 and 19-25 are pending in this application.

Amended claim

Claims 15, 17 and 19-25 have been amended in several particulars for purposes of clarity and brevity that are unrelated to patentability and prior art rejections while Claims. Support for these amendments can be found throughout the specification, particularly in the original claims, examples and figures. No new matter has been added. Accordingly, Applicants respectfully request entry of the amended claims 15, 17, and 19-25.

Summary of the Office Action

In the Office Action, Claims 15, 17, 19-21 and 23-25 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Dorval et al., U.S. Patent No. 5,561,045 and Mattiasson, American Chemical Society Symposium Series. 1979. Vol. 106, Chapter 14 , pp 2-3-220 in view of Hanke, DE 100 00 322A1.

Claims 15, 20 and 22-23 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Dorval et al., U.S. Patent No. 5,561,045, Mattiasson, American Chemical Society Symposium Series. 1979. Vol. 106, Chapter 14 , pp 2-3-220 and

Hanke, DE 100 00 322A1, as applied to claims 15 and 20 above, and further in view of La Scola et al., Journal of Clinical Microbiology, 1996; 34(9): 2270-2274.

First Rejection under 103 (a)

Claims 15, 17, 19-21 and 23-25 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Dorval et al., U.S. Patent No. 5,561,045 and Mattiasson, American Chemical Society Symposium Series. 1979. Vol. 106, Chapter 14 , pp 2-3-220 in view of Hanke, DE 100 00 322A1. This rejection is respectfully traversed, however. Applicants respectfully submit that features of Applicants' claims 7-13 are not disclosed or suggested by Dorval et al. or Mattiason et al. or Hanke, whether taken individually or in combination with any other references of record. Therefore, Applicants respectfully request the Examiner to reconsider and withdraw this rejection for the following reasons.

Gist of claimed invention

The present invention is directed to an in vitro serological diagnosis method for detecting the presence of antibodies specific to an infectious microbial agent in a sample to be tested, the method comprises: (a) depositing, on a solid substrate, a first antigen (Ag_1) of a whole *Staphylococus aureus* bacterium containing protein A, and at least one second antigen (Ag_2)which is characteristic of an infectious microbial agent; (b) contacting said first antigen (Ag_1) and said at least one second antigen (Ag_2) with a sample to be tested, thereby causing said first antigen (Ag_1) and said at least one second (Ag_2) to react with the sample to be tested; and (c) detecting whether a human

immunoglobulin (Ac_1) in the sample reacts with said first antigen (Ag_1) by causing a reaction product (Ag_1-Ac_1), formed from the reaction of said human immunoglobulin (Ac_1) and said first antigen (Ag_1), to react with a detection substance (Ac_2), wherein said detection substance (Ac_2) is an anti-human immunoglobulin which reacts with said human immunoglobulin (Ac_1) in the sample, but does not react with said protein A, so as to control that the sample to be tested contains a human serum. The anti-human immunoglobulin is an immunoglobulin of an animal origin which is a goat immunoglobin or a chick immunoglobulin.

The in vitro serological diagnosis method of the present invention further comprises: performing a series of tests at increasing dilutions of the sample to be tested with the detection substance (Ac_2), which is an anti-human immunoglobulin conjugated with a fluorescent substance, and verifying whether a reaction product (Ag_1-Ac_1-Ac_2), formed by the reaction of the human immunoglobulin (Ac_1), the first antigen (Ag_1), and the detection substance (Ac_2), can be detected by fluorescence at a dilution of the sample to be tested of 1/200 or less. The infectious microbial agent is a micro-organism selected from a bacterium, a virus, a parasite or a fungus.

The second antigen Ag_2 is an intracellular bacterium or a virus. The second antigen Ag_2 can be a bacterium selected from one of *Rickettsia, Coxiella, Bartonella, Tropheryma, Ehrlichia, Chlamydia, Mycoplasma, Treponema, Borrelia,* and *Leptospira*. The second antigen Ag_2 can also be a bacterium responsible for endocarditis. The second antigen Ag_2 can further be a viral antigen selected from a human immunodeficiency virus, a cytomega virus or Epstein-Barr viruses.

The present invention is also directed to a diagnosis kit for detecting the presence of antibodies specific to an infectious microbial agent in a sample to be tested, the diagnosis kit comprising: a solid substrate having deposited thereon, a first antigen (Ag_1) of a whole *Staphylococus aureus* bacterium containing protein A , and a second antigen (Ag_2) which is characteristic of an infectious microbial agent; and at least one reagent which permits detection of the presence of a reaction product (Ag_1-Ac_1) of said first antigen (Ag_1) with a human immunoglobulin (Ac_1) in the sample to be tested, and reaction of the reaction product (Ag_1-Ac_1) with a detection substance (Ac_2), which is an anti-human immunoglobulin that reacts with said human immunoglobulin (Ac_1) in the sample to be tested, but does not react with protein A, so as to control that the sample to be tested contains a human serum.

Applicants respectfully submit that there is nothing in the cited references, Doval et al. or Mattiasson or Hanke that teaches or suggests the advantages of the claimed invention, i.e., the prevention of growth disorder. The present invention is entirely different from the teaching disclosed in the cited references, and moreover, one of ordinary skill in the art would not have any reasons to use the teaching of Doval et al. or Mattiasson or Hanke to make a neuron culture substrate that has a cell-growth suppression region of neurons as claimed in the present invention.

In order to establish a prima facie case of obviousness under 35 U.S.C. §103, the Examiner must show that the prior art reference (or references when combined) must teach or suggest all the claim limitations, and that there must be clear articulation of the reasons why the claimed invention would have been obvious. In other words, all

the claim limitations must be disclosed or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USQP 494, 496 (CCPA 1970). The Supreme Court in KSR International Co. v. Teleflex Inc., 550 U.S. ___, 82 USPQ2d 1385 (2007) also noted that the analysis supporting a rejection under 35 U.S.C. §103 should be made explicit. The Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). See also KSR, 550 U.S. at ___, 82 USPQ2d at 1396 (quoting Federal Circuit statement with approval). Moreover, the Examiner "cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1780, 1783 (Fed. Cir. 1988); otherwise, the Examiner has improperly used Applicants' disclosure as an instruction book on how to reconstruct to the prior art to arrive at Applicants' claimed invention. Furthermore, any deficiencies of the cited references cannot be remedied by general conclusions, without evidence in the record, about what is "basic knowledge" or "common sense". In re Sang Su Lee, No. 00-1158 (Fed. Cir. 2002).

Cited prior art references

Although the Examiner acknowledges that neither cited reference teaches all features of the claim in the Office Action, the Examiner contends that the present

invention is rendered obvious by the combination of the prior art. Specifically, the Examiner alleges that:

> [it] would have been prima facie obvious at the time of applicants invention to modify the *in vitro* serological diagnosis method in which, in a sample to be tested, the presence is detected of antibodies specific to an infectious microbial agent, as taught by Dorval et al., wherein the modifications incoroporate using deposited whole *S. aureus* bacterium comprising protein A as taught by Mattiasson and the use [of] a control zone as taught by Hanke in order to provide a method that establishes detection of human immunoglobulin interaction. Further, there is a reasonable expectation of success in incorporating the methods of Dorval et al., Mattiasson and Hanke since they teach providing a sample to be tested is [reacted] with solid-substrate having a deposited first and second antigen and detecting whether the human immunoglobulin reacts with the antigen, especially when no change in their respective functions, thus the combination could have yielded predictable results to one of ordinary skill in the art at the time of the invention. Furthermore, one of ordinary skill in the art at the time the invention was made would have been motivated to extend the methods taught by Dorval et al., Mattiasson and Hanke while incorporating the additional whole cell bacterial and viral pathogens into the *in vitro* serological diagnosis as in order to arrive at the claimed invention with provide assays containing serum and conjugate control zones when detecting infectious microbial antigens.

Applicants respectfully traverse.

No motivation to combine

Applicants respectfully submit that not only there is nothing in either the Dorval et al. document or the Mattiasson document or the Hanke document that teaches or suggests the claimed invention, one of ordinary skill would not be motivated to combine the teachings of these three documents to make the present invention at the time it was produced by the present inventors because none of the cited documents teaches or suggests a non labeled protein A immobilized on solid support used in combination with

a detection substance raised so that it does not react with protein A as recited in the claims of the present invention.

Applicants respectfully submit that Applicants respectfully submit that the Dorval et al. document is directed to only protein A, and not the whole *Staphylococcus aureus* bacterium. As for the Mattiasson document, this document is directed to a very old teaching of immobilizing whole cells published in 1979. There is nothing in the Mattiasson document that teaches or suggests utilizing a whole *S. aureus* bacterium as a control antigen in combination with the detection substance of the claimed invention.

With regard to the Hanke document, this document is directed to strips for Western blotting using labeled conjugated animal antibody which is specific for human immunoglobulin. There is nothing in the Hanke document that teaches or suggests the use of a labeled animal antibody which does not react with protein A in combination with a none labeled protein A (whole *S. aureus*) immobilized on a solid support as recited in the claims of the present invention.

Hence, Applicants respectfully submit that at the time the invention was made, one of ordinary skill in the art would not have been motivated to modify the teaching of Dorval et al. by (1) substituting a protein A with a whole *S. aureus* bacterium of Mattiasson because Mattiason's technique does not teach or suggest utilizing a whole *S. aureus* bacterium as a control antigen in combination with the detection substance of the claimed invention, and (2) utilizing a control zone of Hanke because Hanke does not teach or suggest the use of a labeled animal antibody which does not react with protein A in combination with a none labeled protein A (whole *S. aureus*) immobilized on a solid

support to make the claimed invention.

In addition, Applicants respectfully submit that in the Dorval et al. document, a blocking agent is used to prevent interaction between protein A and anti-Iga IgG or anti-IgM IgG. Please see column 4, lines 13-15 of Dorval et al. where Dorval clearly discloses that there is an evidence that the concerned anti-IgA IgG and anti-IgM IgG have not been raised so that they don't react with protein A. Therefore, at most Dorval et al. teach away from the claimed invention.

Hence, one of ordinary skill in the art would have no motivation to combine the teaching away of Dorval with the teaching of Mattiasson and Hanke to make the claimed invention.

Further detail supports as to why one of ordinary skill in the art would not be motivated to combine the teachings of Dorval et al., Mattiasson, and Hanke to make the claimed invention are presented below.

Dorval et al.

In the Office Action, the Examiner maintains that Dorval teaches the "addition of the detection agent which is labeled antihuman immunoglobulin which does not react with protein A, see figures 1A-1P". The Examiner also maintains that Dorval et al. can be distinguish from claim 15 only because Dorval et al. do not specifically teach immobilization of a whole *S. aureus* bacterium.

However, Applicants respectfully submit that it is noted that the Examiner has not responded to the very complete and detailed development provided in the last response wherein it has been fully explained that, in DORVAL, protein A is a labeled protein used

as a detection substance in combination with other anti-IgA IgG and anti-IgM IgG immunoglobulins as detection substances.

Applicants respectfully submit that nowhere, in the Dorval et al. document is there any teaching or suggestion of an in vitro serological diagnosis method for detecting a presence of antibodies specific to an infectious microbial agent in a sample to be tested comprising a non labeled *Staphylococcus aureus* bacterium (therefore a non labeled protein A) immobilized on a solid support in combination with antihuman immunoglobulin raised so that it does not react with protein A.

Applicants respectfully submit that in the Dorval et al. document, a blocking agent is used to prevent interaction between protein A and anti-Iga IgG or anti-IgM IgG. Please see column 4, lines 13-15 of Dorval et al. where Dorval clearly discloses that there is an evidence that the concerned anti-IgA IgG and anti-IgM IgG have not been raised so that they don't react with protein A. Therefore, at most Dorval et al. teach away from the claimed invention.

In addition, Applicant respectfully submit that Dorval et al. do not teach or suggest that the anti-human immunoglobulin is a goat or chicken antihuman immunoglobulin as recited in claim 17. Applicants respectfully submit that goat and chicken antihuman immunoglobulin has the advantageous property of not reacting with protein A.

Applicants also respectfully submit that the use of the whole *Staphylococcus aureus* bacterium is advantageous because it is a corpuscular antigen control which is easier and relieable to adsorb onto a solid substrate when deposited thereon. The use

of the whole *Staphylococcus aureus* bacterium is also advantageous because the detection by visualisation of a corpuscular control agent is much more reliable and easier to detect than the visualization of an immunological reaction between an immunoglobulin and a purified protein adsorbed on a solid substrate, especially with a fluorescent marking.

Applicants also respectfully submit that there is nothing in the Dorval et al. document that teaches or suggests a detection substance that is an immunoglobulin which is raised against any kind of human immunoglobulin but does not react with protein A as recited in the present claims. There is nothing, in the Dorval document that teaches or suggests that the claimed detection substance is an immunoglobulin which is raised against any kind of human immunoglobulin (Iga + IgM + IgG + IgE+ etc) and which is raised so that it does not react with protein A.

Applicants respectfully submit that the use of an antihuman immunoglobulin as detection substance, according to the present invention, is advantageous in respect to the use of a labeled protein A as disclosed in Dorval et al., because, according to the present invention, a second immobilized antigen Ag_2 must be detected and the labeled protein A would be unable to detect anti-Ag_2 IgM in the event where the presence of such anti-Ag_2 IgM immunoglobulin would be tested (protein A would be able to bind only to anti-Ag_2 IgG). Applicant also respectfully submit that ndigo serves both as a label and a blocking agent, blocking the binding site on each anti-IgA IgG and anti-IgM IgG with protein A.

Further, Applicants respectfully submit that using protein A as a detection

substance in the process of the invention is less relieable than using an antihuman immunoglobulin as a detection substance for the further reason that for detecting the complex Ag_1-human IgG fixed to the solid support (wherein Ag_1 = Staphylococcus bascteria), the labeled protein A would enter in competition with the protein A of the Staphylococcus bacteria immobilized onto the solid support. Therefore, protein A (as a detection substance) would react less efficiently with the human immunoglobulin bound to the Staphylococcus bacteria immobilized onto solid support. Accordingly, antihuman immunoglobulins are preferred as a detection substance because they bind to human immunoglobulin through a different binding site than the binding site of human IgG with protein A of Staphylococcus bacteria.

Applicants respectfully submit that Dorval et al. is directed to a method and kit that is different from the claimed invention as recited above and acknowledged by the Examiner. Applicants respectfully submit that the Dorval et al. document is directed to a method for simultaneously detecting immunoglobulins including IgG, IgA and/or IgM in a single test assay so that if any of these immunoglobulins have been produced in response to a particular infection agent, such production could be detected which is different from the claimed invention.

In the Office Action, the Examiner alleges that Figure 1A-1F of Dorval et al. teach a solid support with the first antigen containing protein A, a second microbial antigen, the addition of the detection agent which is labeled antihuman immunoglobulin which does not react with protein A. Applicants respectfully submit that this allegation is not supported by the Dorval et al. document. Applicants respectfully submit that this

allegation this is not taught nor suggested by the Dorval et al. document for the reasons presented below and as set forth in columns 10 and 11 of the Doral et al. document. Applicants respectfully submit that in contradiction to the Examiner's allegation, Figures 1A-1F clearly state that a labeled protein A is used as a detecting substance. Column 11, lines 18-19 of the Dorval et al. document clearly states that "according to the assay, the detection reagent includes protein A (36) coupled to a hydrophobic label, specifically indigo."

Applicants respectfully submit that although protein A is immobilized on a support solid, this immobilized protein A reacts with IgG of all specificities present in the sample (see figure 1B) and the detection substance between immobilized protein A and IgG (see figure 1C) is protein A labeled with indigo (36) to detect the reaction product PA-IgG. Applicants also respectfully submit that according to the Dorval et al. document, labeled protein A is used in combination with two other detection reagents as shown in Figures 1C, and as recited in column 11, line 21: "the reagent also includes anti-IgA-IgG 38...and anti-IgM-IgG 40...indigo is coupled to each of anti-IgA-IgG 38 and anti-IgM-IgG 40...".

Applicants respectfully submit that the Dorval et al. document is directed to detecting simultaneously immunoglobulins including IgG, IgA and/or IgM in a single test assay so that if any of these imunoglobulins have been produced in response to a particular infection agent, such production could be detected. Applicants respectfully submit that according to the Dorval et al. document, a labeled protein A is used to determine the presence of IgG while labeled anti-IgA-IgG or labeled anti-IgM-IgG is

used to determine the presence of IgA or, respectively, IgM. However, when such agents are used together, the labeled protein A can bind to the labeled anti-IgA-IgG and anti-IgM-IgG. (See column 5, lines 50-62 of the Dorval et al. document).

Applicants respectfully submit that column 10, lines 24, 25, 26 of the Dorval et al. document clearly recites that "the invention is useful whenever it is desirable to prevent the interaction of two detection reagents with one another". According to Dorval et al., a blocking agent is used to prevent interaction between the two detection reagents, namely protein A and anti-IgA-IgG or anti-IgM-IgG. Applicants also respectfully submit that column 10, lines 2-3 of the Dorval et al. document clearly recites that "preferably, these labeled immunoglobulins are blocked with the label itself and the detection reagent includes labeled protein A, labeled and blocked anti-IgA-IgG and labeled and blocked ani-IgM-IgG. According to the assay of Dorval et al., the detection reagent includes protein A 36 coupled to a hydrophobic label, specifically indigo, which binds to IgG bound to protein A at area 12 of surface 10 and to IgG bound to HIV at area 16 of surface 10. The reagent also includes anti-IgA-IgG 38 which binds to IgA bound to IgV at area 16 of surface 10 and anti-IgM-IgG 40 which binds to IgM bound to HIV at area 16 of surface 100. More specifically, as specified in column 11, lines 24-27, "indigo (the label) is coupled to each of anti-IgA-IgG 38 and anti-IgM-IgG 40, serving both as a label and a blocking agent blocking the biding site of each from interaction with a protein A."

In view of the above, Applicants respectfully submit that Dorval et al. neither teach nor suggest the claimed invention. At most, Dorval et al. teach away from the present invention. There is nothing in the Dorval et al. document that teaches or

suggests an in vitro serological diagnosis method for detecting the presence of antibodies specific to an infectious microbial agent in a sample to be tested comprising a step of depositing, on a solid substrate, a first antigen (Ag_1) of a whole *Staphylococus aureus* bacterium containing protein A, and at least one second antigen (Ag_2)which is characteristic of an infectious microbial agent, let alone a step of contacting said first antigen (Ag_1) and said at least one second antigen (Ag_2) with a sample to be tested, thereby causing said first antigen (Ag_1) and said at least one second (Ag_2) to react with the sample to be tested; and further let alone a step of detecting whether a human immunoglobulin (Ac_1) in the sample reacts with said first antigen (Ag_1) by causing a reaction product (Ag_1-Ac_1), formed from the reaction of said human immunoglobulin (Ac_1) and said first antigen (Ag_1), to react with a detection substance (Ac_2), wherein said detection substance (Ac_2) is an anti-human immunoglobulin which reacts with said human immunoglobulin (Ac_1) in the sample, but does not react with said protein A, so as to control that the sample to be tested contains a human serum as recited in the claims of the present invention.

Mattiasson

With regard to the Mattiason document, Applicants respectfully submit that this document does not teach nor suggest to use the whole Staphylococcus aureus bacterium as a control antigen in combination with the detection substance such as recited in the claims of the present invention.

Applicants respectfully submit that the Mattiasson document is directed to a very old teaching of immobilizing whole cells published in 1979. There is nothing in the

Mattiasson document that teaches or suggests utilizing a whole *S. aureus* bacterium as a control antigen in combination with the detection substance of the claimed invention.

Mattiasson teaches that immobilized cells can either be used as sensors in analytical system or by being kept in close proximity to a transducer. The immobilized cells of Mattiasson are used to evaluate the effect a certain substance or group of substances may exert on living cells. In sum, the Mattiasson document is directed to immobilized cells used to study cells, cell metabolism, cell physiology and cell toxicology.

There is nothing in the Mattiasson document that teaches or suggests an in vitro serological diagnosis method for detecting the presence of antibodies specific to an infectious microbial agent in a sample to be tested comprising a step of depositing, on a solid substrate, a first antigen (Ag_1) of a whole *Staphylococus aureus* bacterium containing protein A, and at least one second antigen (Ag_2)which is characteristic of an infectious microbial agent, let alone a step of contacting said first antigen (Ag_1) and said at least one second antigen (Ag_2) with a sample to be tested, thereby causing said first antigen (Ag_1) and said at least one second (Ag_2) to react with the sample to be tested; and further let alone a step of detecting whether a human immunoglobulin (Ac_1) in the sample reacts with said first antigen (Ag_1) by causing a reaction product (Ag_1-Ac_1), formed from the reaction of said human immunoglobulin (Ac_1) and said first antigen (Ag_1), to react with a detection substance (Ac_2), wherein said detection substance (Ac_2) is an anti-human immunoglobulin which reacts with said human immunoglobulin (Ac_1) in the sample, but does not react with said protein A, so as to control that the sample to

be tested contains a human serum as recited in the claims of the present invention.

Hanke

With regard to the Hanke document, this document is directed to strips for Western blotting using labeled conjugated animal antibody which is specific for human immunoglobulin. There is nothing in the Hanke document that teaches or suggests the use of a labeled animal antibody which does not react with protein A in combination with a none labeled protein A (whole *S. aureus*) immobilized on a solid support as recited in the claims of the present invention.

Applicants also respectfully submit that there is nothing in the Hanke document that teaches or suggests a detection substance that is an immunoglobulin which is raised against any kind of human immunoglobulin but does not react with protein A as recited in the present claims. In addition, Applicants respectfully submit that the use of goat and chicken antihuman immunoglobulins, as recited in claim 17, has advantageous properties that are neither taught nor disclosed in the prior art documents. These advantageous properties include the ability of not reacting with protein A.

Applicants further respectfully submit that there is nothing, in the Hanke document that teaches or suggests that the claimed detection substance is an immunoglobulin which is raised against any kind of human immunoglobulin (Iga + IgM + IgG + IgE+ etc) and which is raised so that it does not react with protein A.

Applicants respectfully submit that Hanke teach a method that is different from the claimed invention. The Hanke document relates to immune-whether-guide-mature. Hanke does not teach or suggest using the entire Staphylococcus aureus as a control

antigen immobilized on a solid support to detect antibodies specific to an infectious microbial agent as claimed in the present invention.

There is nothing in the Hanke document that teaches or suggests an in vitro serological diagnosis method for detecting the presence of antibodies specific to an infectious microbial agent in a sample to be tested comprising a step of depositing, on a solid substrate, a first antigen (Ag_1) of a whole *Staphylococus aureus* bacterium containing protein A, and at least one second antigen (Ag_2)which is characteristic of an infectious microbial agent, let alone a step of contacting said first antigen (Ag_1) and said at least one second antigen (Ag_2) with a sample to be tested, thereby causing said first antigen (Ag_1) and said at least one second (Ag_2) to react with the sample to be tested; and further let alone a step of detecting whether a human immunoglobulin (Ac_1) in the sample reacts with said first antigen (Ag_1) by causing a reaction product (Ag_1-Ac_1), formed from the reaction of said human immunoglobulin (Ac_1) and said first antigen (Ag_1), to react with a detection substance (Ac_2), wherein said detection substance (Ac_2) is an anti-human immunoglobulin which reacts with said human immunoglobulin (Ac_1) in the sample, but does not react with said protein A, so as to control that the sample to be tested contains a human serum as recited in the claims of the present invention.

Combined teaching of Dorval et al., Mattiasson, and Hanke

Applicants respectfully submit that none of the cited documents teaches or suggests a non labeled protein A immobilized on solid support used in combination with a detection substance raised so that it does not react with protein A as recited in the claims of the present invention.

In view of the above, Applicants respectfully submit that not only there is nothing in either the Dorval et al. document or the Mattiasson document or the Hanke document that teaches or suggests the claimed invention, one of ordinary skill would not be motivated to combine the teachings of these three documents to make the present invention at the time it was produced by the present inventors. There is nothing in the Dorvel et al. document or Mattiasson document or Hanke document either alone or in combination thereof that teaches or suggests an in vitro serological diagnosis method for detecting the presence of antibodies specific to an infectious microbial agent in a sample to be tested comprising a step of depositing, on a solid substrate, a first antigen (Ag_1) of a whole *Staphylococus aureus* bacterium containing protein A, and at least one second antigen (Ag_2)which is characteristic of an infectious microbial agent, let alone a step of contacting said first antigen (Ag_1) and said at least one second antigen (Ag_2) with a sample to be tested, thereby causing said first antigen (Ag_1) and said at least one second (Ag_2) to react with the sample to be tested; and further let alone a step of detecting whether a human immunoglobulin (Ac_1) in the sample reacts with said first antigen (Ag_1) by causing a reaction product (Ag_1-Ac_1), formed from the reaction of said human immunoglobulin (Ac_1) and said first antigen (Ag_1), to react with a detection substance (Ac_2), wherein said detection substance (Ac_2) is an anti-human immunoglobulin which reacts with said human immunoglobulin (Ac_1) in the sample, but does not react with said protein A, so as to control that the sample to be tested contains a human serum as recited in the claims of the present invention.

Therefore, Applicants respectfully submit that at the time the invention was

made, one of ordinary skill in the art would not have been motivated to modify the teaching of Dorval et al. by (1) substituting a protein A with a whole *S. aureus* bacterium of Mattiasson because Mattiason's technique does not teach or suggest utilizing a whole *S. aureus* bacterium as a control antigen in combination with the detection substance of the claimed invention, and (2) utilizing a control zone of Hanke because Hanke does not teach or suggest the use of a labeled animal antibody which does not react with protein A in combination with a none labeled protein A (whole *S. aureus*) immobilized on a solid support to make the claimed invention.

In addition, Applicants respectfully submit that in the Dorval et al. document, a blocking agent is used to prevent interaction between protein A and anti-Iga IgG or anti-IgM IgG. Please see column 4, lines 13-15 of Dorval et al. where Dorval clearly discloses that there is an evidence that the concerned anti-IgA IgG and anti-IgM IgG have not been raised so that they don't react with protein A. Therefore, at most Dorval et al. teach away from the claimed invention.

Hence, one of ordinary skill in the art would have no motivation to combine the teaching away of Dorval with the teaching of Mattiasson and Hanke to make the claimed invention.

In view of all the differences and advantages of the claimed present invention discussed above, Applicants respectfully submit that one of ordinary skill in the art would be motivated to utilize the teaching of Dorval et al. either alone or in combination with Mattiasson and Hanke at the time of the invention was invented to modify the method taught by Dorval et al. to arrive at the claimed invention in order to provide an easy

control test of the presence of a human serum in the sample tested in the serological diagnosis method.

Thus, Applicants respectfully request reconsideration and withdrawal of this rejection.

Second Rejection under 35 USC § 103

In addition, claims 15, 20 and 22- 23 have been rejected under 35 USC § 103 (a) for being unpatentable over Dorval et al., Mattiason, and Hanke as applied to claims 15 and 20 in view of La Scola et al. (Journal of Clinical Microbology, 1996; 34(9): 2270-2274). Applicants respectfully traverse.

As discussed above, Applicants respectfully submit that neither the Dorval et al. document nor the Mattiasson document or the Hanke document teaches or suggests the use of the entire *Staphylococcus aureus* bacterium to detect the presence of antibodies specific to an infectious microbial agent as recited in the claims of the present invention. Furthermore, none of the cited documents teaches or suggests a non labeled protein A immobilized on solid support used in combination with a detection substance raised so that it does not react with protein A as recited in the claims of the present invention.

There is nothing in the Dorvel et al. document or Mattiasson document or Hanke document either alone or in combination thereof that teaches or suggests an in vitro serological diagnosis method for detecting the presence of antibodies specific to an infectious microbial agent in a sample to be tested comprising a step of depositing, on a solid substrate, a first antigen (Ag_1) of a whole *Staphylococus aureus* bacterium

containing protein A, and at least one second antigen (Ag_2)which is characteristic of an infectious microbial agent, let alone a step of contacting said first antigen (Ag_1) and said at least one second antigen (Ag_2) with a sample to be tested, thereby causing said first antigen (Ag_1) and said at least one second (Ag_2) to react with the sample to be tested; and further let alone a step of detecting whether a human immunoglobulin (Ac_1) in the sample reacts with said first antigen (Ag_1) by causing a reaction product (Ag_1-Ac_1), formed from the reaction of said human immunoglobulin (Ac_1) and said first antigen (Ag_1), to react with a detection substance (Ac_2), wherein said detection substance (Ac_2) is an anti-human immunoglobulin which reacts with said human immunoglobulin (Ac_1) in the sample, but does not react with said protein A, so as to control that the sample to be tested contains a human serum as recited in the claims of the present invention.

As for the La Scola et al. document, this document cannot be used to cure the deficiencies of the Dorval et al. document.

Applicants respectfully submit that La Scola et al. disclose serological cross-reactions between *Bartonella quintana, Bartonella henselae,* and *Coxiella burnetti.*

Applicants respectfully submit that La Scola et al. neither teach nor suggest a method or kit for detecting the presence of antibodies specific to an infectious microbial agent in a sample to be tested using a whole *Staphylococcus aureus* as recited in the claims of the present invention. Further, the La Scola et al. document neither teaches nor suggests a method comprising (a) depositing on a solid substrate a first antigen Ag_1 comprising a whole Staphylococcus aureus bacterium and at least one second antigen Ag_2; (b) contacting said first antigen Ag_1 and said at least one second antigen Ag_2 with a

sample to be tested causing said first antigen Ag_1 and said at least one second Ag_2 to react with a sample to be tested; (c) detecting whether a human immunoglobulin Ac_1 in said human serum reacts with said first antigen Ag_1 by causing the reaction product Ag_1-Ac_1 to react with a detection substance; and (d) providing a controlled sample containing a human serum to be tested for detecting whether said human immunoglobulin react with said detection substance has reacted with the reaction product as recited in the claims of the present invention.

Therefore, one of ordinary skill in the art would not be motivated to combine the teaching of Dorval et al., Mattiasson Hanke with the teaching of La Scola et al. to make the present invention.

Applicants respectfully submit that at the time the invention was made, one of ordinary skill in the art would not have been motivated to modify the teaching of Dorval et al. by (1) substituting a protein A with a whole *S. aureus* bacterium of Mattiasson because Mattiason's technique does not teach or suggest utilizing a whole *S. aureus* bacterium as a control antigen in combination with the detection substance of the claimed invention, (2) utilizing a control zone of Hanke because Hanke does not teach or suggest the use of a labeled animal antibody which does not react with protein A in combination with a none labeled protein A (whole *S. aureus*) immobilized on a solid support, and (3) substituting a wide variety of agents as taught by La Scola et al. to make the claimed invention.

In addition, Applicants respectfully submit that in the Dorval et al. document, a blocking agent is used to prevent interaction between protein A and anti-Iga IgG or anti-

IgM IgG. Please see column 4, lines 13-15 of Dorval et al. where Dorval clearly discloses that there is an evidence that the concerned anti-IgA IgG and anti-IgM IgG have not been raised so that they don't react with protein A. Therefore, at most Dorval et al. teach away from the claimed invention.

Hence, one of ordinary skill in the art would have no motivation to combine the teaching away of Dorval with the teaching of Mattiasson, Hanke, and La Scola et al. to make the claimed invention.

In view of all the differences and advantages of the claimed present invention discussed above, Applicants respectfully submit that one of ordinary skill in the art would be motivated to utilize the teaching of Dorval et al. either alone or in combination with Mattiasson, Hanke, and La Scola et al. at the time of the invention was invented to modify the method taught by Dorval et al. to arrive at the claimed invention in order to provide an easy control test of the presence of a human serum in the sample tested in the serological diagnosis method.

Thus, Applicants respectfully request reconsideration and withdrawal of this rejection.

CONCLUSION

In light of the foregoing Remarks, Applicants respectfully submit that the application is now in condition for examination.

Should any minor matter remain, or should the Examiner feel that an interview would expedite the prosecution of this application, the Examiner is invited to call the undersigned to arrange such.

To the extent necessary, Applicant petitions for an extension of time under 37 CFR 1.136. Please charge any shortage in the fees due in connection with the filing of this paper, including extension of time fees, to the deposit account of Antonelli, Terry, Stout & Kraus, LLP, Deposit Account No. 01-2135 (Case: 935.44544X00), and please credit any excess fees to such deposit account.

Respectfully submitted,

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